

Emerging and Re-emerging Infectious Diseases: A Continuous Challenge




Mosquito-borne virus

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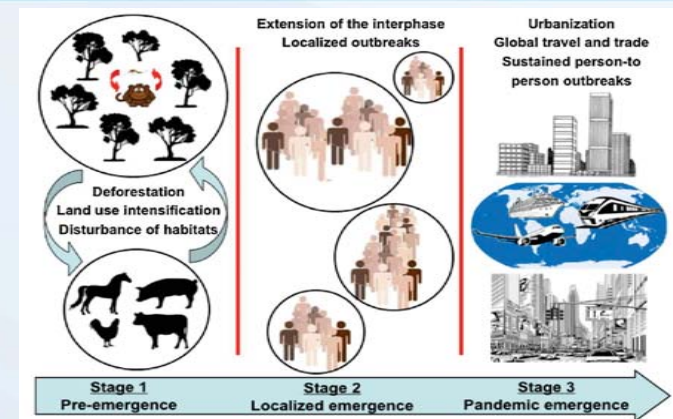
Outline

- Global burden of mosquito-borne virus
- Challenges of management
- Prevention and control

Mosquito-borne virus disease

	Vector	Family, genus	Pathogen
<i>Aedes aegypti</i>	<i>A. albopictus</i>	<i>Flaviviridae, Flavivirus</i>	Yellow fever virus
			Dengue virus
		<i>Togaviridae, Alphavirus</i>	Zika virus
			Chikungunya virus
	<i>Culex</i> spp.	<i>Flaviviridae, Flavivirus</i>	Japanese encephalitis virus, West Nile virus, SLE
		<i>Togaviridae, Alphavirus</i>	WEE, EEE, VEE

Factors associated with arbovirus emergence



Dengue virus: endemic in 152 countries (70% in Asia)
400 million infection, 100 million symptomatic, 20,000 deaths

Zika virus: endemic to 87 countries



Chikungunya virus: endemic in 111 countries,
> 10 million cases

Japanese encephalitis: endemic to 32 countries

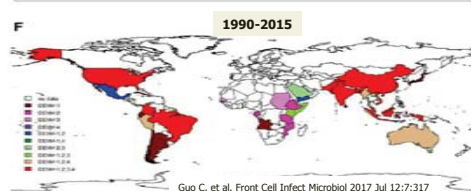
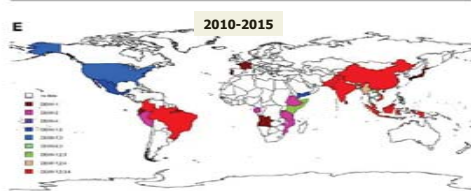
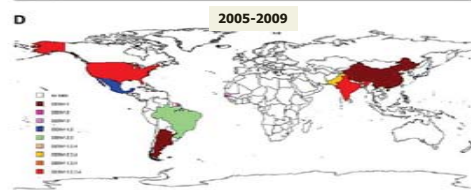
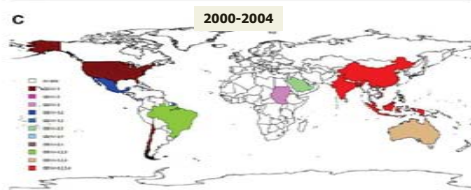


Annual Disease rates per 100,000 population
Not Endemic: >0 to 1 >1 to 20 >20 to 100 >100 to 500 >500

Annual Disease rates per 100,000 population
Not Endemic: >0 to 0.001 >0.001 to 0.1 >0.1 to 0.5 >0.5 to 2 >2

Sukhralia S, et al. Eur J of Clin Microbiol & Infect Dis (2019) 38:3–14

DENGUE VIRUS



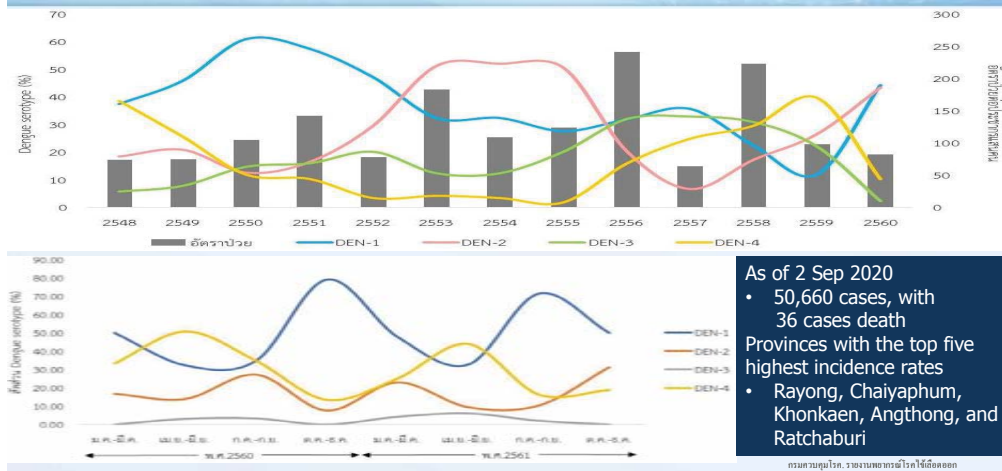
Guo C, et al. Front Cell Infect Microbiol 2017 Jul 12;7:317

Global dengue situation in 2019

- PAHO data from January to October 2019
 - 2.7 million cases and 1206 deaths in Brazil, Mexico, Guatemala, Colombia, Honduras, Paraguay
 - More than 22,000 were severe dengue
- SEA Region (> 50,000 cases)
 - Bangladesh, Indonesia, Sri Lanka, Thailand
- Western Pacific Region (> 50,000 cases)
 - Malaysia, Philippines and Viet Nam, Singapore
- Eastern Mediterranean Region
 - Pakistan, Sudan, Yemen

European Centre for Disease Prevention and Control: <https://www.ecdc.europa.eu/en/dengue-monthly>

Burden of dengue in Thailand



Compared CKV, ZKV and dengue virus

Parameters	Chikungunya	Zika	Dengue
Genus	<i>Alphavirus</i>	<i>Flavivirus</i>	<i>Flavivirus</i>
Symptomatic case	85%	15-20%	15-20%
Fever	++	+/-	+++
Headache	+	+	+++
Myalgia	++	+	+++
Maculopapular rash	++	+++	+
Arthralgia	+++	+	+/-
Non-purulent conjunctivitis	++	+++	-
Neutropenia	+	-	++
Thrombocytopenia	+/-	+/-	+++
Shock syndrome	-	-	+++
Complications	Chronic arthralgia/arthrititis	GBS, Microcephaly	DSS
Lab diagnosis	PCR, serology	PCR (serum, urine)	PCR, serology

Musso D, et al. Clin Microbiol Rev 2016; 29:487-524; Shuaib et al. The American Journal of Medicine 2016.

Treatment for Dengue

- Supportive and symptomatic treatment
 - Paracetamol: RCT of 125 patients: 500 mg every 4 hours vs. placebo → higher rate of transaminase elevation (22% vs. 10%)
 - Sufficient fluid replacement for 48–72 h during critical phase until the vasculopathy reverses
 - Avoid NSAIDs until afebrile for ≥ 48 hours and no warning signs
- No specific antiviral treatment
 - Chloroquine, Balapiravir (no change in viremia and NS1 antigenemia)
 - Celgosivir, Lovastatin (no change in viremia and NS1 antigenemia)
 - Ivermectin (ESIDEN): reduction in serum NS1 antigenemia

Lancet Global Health. 2019; 7: e664-e670; Low JG, et al. JID. 2017;215(S2):S96-102; Suputtamongkol Y, et al. CID (in press)

Challenges of dengue

- Outbreak increasing worldwide: reported case > 8 fold over 2 decades
 - 505,430 in 2000 → > 2.4 million in 2010 → 4.2 million in 2019
- WHO include dengue in top 10 public health threats in 2019
- Mortality and morbidity should reduce by 50% and 25%, respectively by 2020 as compared to 2010
 - Early case detection
 - Need to distinguish with other tropical infections
 - Delay diagnosis in patients with negative NS1 or uncommon feature (eg. expanded dengue syndrome)

WHO: Dengue and severe dengue 2020

Challenges of dengue

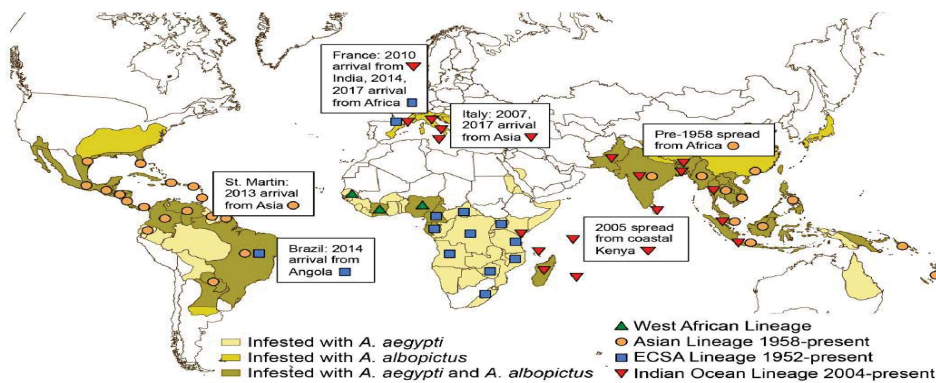
- Improve management of severe case
- Require strengthening of vector control measures
- Live-attenuated dengue vaccine: Dengvaxia® (CYD-TDV)
 - Approved in 20 countries only in individuals 9 -45 years with laboratory-confirmed previous dengue and living in endemic areas

WHO: Dengue and severe dengue 2020



CHIKUNGUNYA VIRUS

Distribution of chikungunya virus



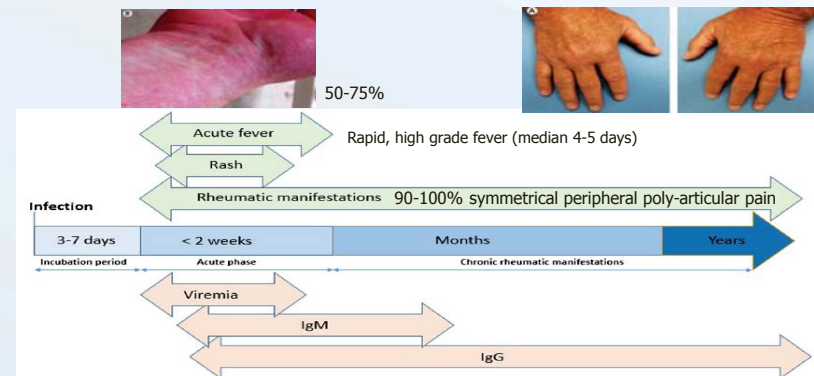
- First isolated in 1953 in Tanzania → Confirmed disease in Asia (Philippines) in 1954
- Spreading of epidemic strain of ECSA lineage from Kenya to India in 2005-6 (>1.3 million infected)
- Initially identified in the western hemisphere in October, 2013
- Oct 2013- Aug 2016: confirmed > 1 million cases in 48 countries in America

PLoS Negl Trop Dis 2019; 13(1):e0006919.



Chikungunya virus infection

- 85% symptomatic with low MR (0.1%) but high morbidities



Lancet Infect Dis 2017;17:e107-17.; Curr Rheumatol Rep (2017) 19: 69; ; J Clin Invest. 2017;127(3):737-749..



Chikungunya virus infection

- Rheumatic manifestation: acute (≤ 2 weeks), subacute, chronic (> 3 months)
- IOL lineage: more severe presentations than Asian genotype
- 2 meta-analysis
 - 43% had symptoms > 3 months, 21% had symptoms > 12 months¹
 - 25% had symptoms > 2 months, 14% had symptoms > 18 months²
- Lost >10 days productivity in $\sim 30\%$ (Bangladesh 2017)
- Independent predictors of chronic disease³
 - Age > 45 , severe initial joint pain, underlying comorbidity and high viremia

Suhrbier A. Nature Reviews Rheumatology 2019; 15: 597–611; 1. Paixao, E. S. et al. Trans. R. Soc. Trop. Med. Hyg 2018. 112, 301–316. 2. Rodriguez- Morales, A. J., et al. Arthritis Care Res. 2016;68:1849–58. 3. van Aalst, M., et al. Travel Med. Infect. Dis. 15, 8–22 (2017).



Situation of CKV infection in 2020

- Asia and the Americas: the most affected
 - Brazil accounted for $>90\%$ in the region of the Americas
- Pakistan faced a persistent outbreak: reported 8,387 cases, while India suffered with 62,000 cases
- Thailand
 - $\sim 11,484$ cases reported in 2019: Pattani, Ranong, Phuket, Tak and Songkhla (> 3 times of 2018)
 - 1 Jan- 21 Aug 2020: 6,888 cases in 68 provinces: Chanthaburi, Uthai Thani, Lamphun and Rayong

WHO: Chikungunya: <https://www.who.int/news-room/fact-sheets/detail/chikungunya>



Treatment of CKV virus diseases

- Supportive and symptomatic for fever and joint pain
 - Paracetamol in acute phase
 - NSAIDs: contraindicated in acute phase, suspected coinfection with dengue, CKD, DM, 6-8 weeks before pregnant
 - Consider DMARDs in chronic phase: HCQ (5MHD), MTX (more severe)
 - Open RCT of persistent CA for >1 year: 139 patients
 - MTX 15 mg/day + sulfasalazine 1 g/day + HCQ 400 mg/day is superior to HCQ monotherapy
 - Prevent functional impairment and iatrogenic complication
- No specific antiviral agents or vaccine

Carlos Alexandre Antunes de Brito, et al. Journal of the Brazilian Society of Tropical Medicine Vol.:53:(e20190517): 2020; Ravindran V, et al. Clin Rheumatol. 2017 Jun;36(6):1335-1340.



Challenges of CKV virus diseases

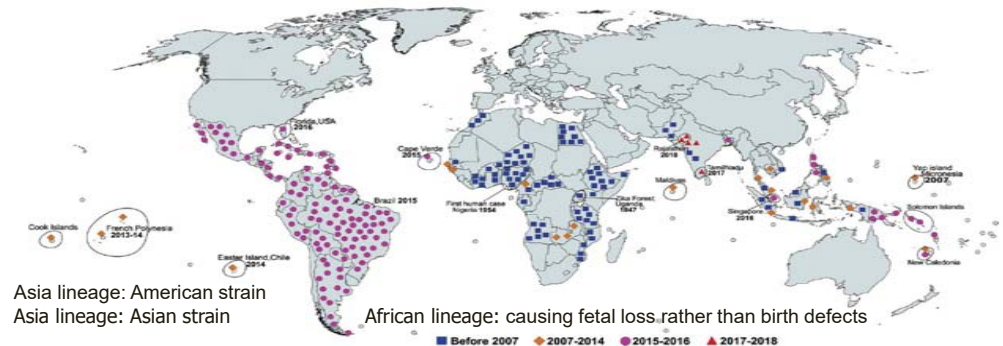
- Complexity of therapeutic management
- Clear need for better treatment options for patients with chikungunya and NSAID- refractory arthropathy, chronic arthralgia or severe, life- threatening disease
- Variations in cross neutralization capacities from different CHIKV genotype—if using single strain to develop vaccine

Suhrbier A. Nature Reviews Rheumatology 2019; 15: 597–611



ZIKA VIRUS

Global distribution of Zika



- Indonesia: 9% of children had evidence of prior ZIKV infection by the age of 5 years
- Lao People's Republic: 10% of asymptomatic adult blood donors in 2015 had evidence of prior ZIKV infection
- Thailand demonstrated seasonal patterns of ZIKV transmission that coincided with those of dengue virus

WHO: Zika epidemiology update as of July 2019; Sharma V, et al. Can. J. Microbiol 2020. 66: 87–98.

Zika virus infection in pregnancy

- Microcephaly
- Congenital Zika virus syndrome
 - Severe microcephaly in which the skull has partially collapsed
 - Decreased brain tissue with a specific pattern of brain damage (subcortical calcifications)
 - Damage to the back of the eye (macular scarring and focal pigmentary retinal mottling)
 - Congenital contractures, such as clubfoot or arthrogryposis



Adverse fetal outcome after ZKV infection

- A prospective study of pregnant women with symptomatic ZIK infection in French territories in the Americas (n=555)

	1 st trimester (n=189)	2 nd trimester (n=252)	3 rd trimester (n=114)	Total (n=555)
Stillborn/ not carried to term	24 (12.7)	4 (1.6)	0	28 (5)
Live-born	165 (87.3)	248 (98.4)	114 (100)	527 (95)
Neurologic/ocular defects	24 (12.7)	9(3.6)	6 (5.3)	38 (7)
• Microcephaly	19 (10.1)	8 (3.2)	5 (4.4)	32 (5.8)
Congenital Zika syndrome	13 (6.9)	3 (1.2)	1 (0.9)	17 (3.1)

Recommendation: first U/S 4 weeks from the suspected exposure, followed by serial U/S every 4 weeks; at least one ultrasound should be performed between 28 and 33 weeks of gestation

N Engl J Med 2018;378:985-94;

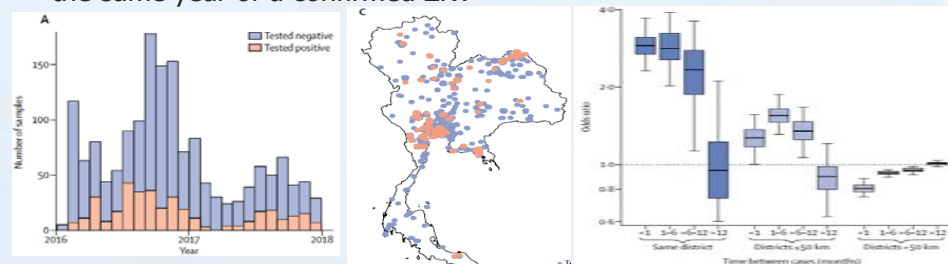
Zika Virus and Guillain–Barre Syndrome

- From 164,237 confirmed/ suspected cases of ZIKV disease in 7 countries in South America, April 1, 2015 to March 31, 2016 → 1474 cases of GBS
 - The incidence: 28% higher in males, increased with age
- Presented with generalized weakness (74%), facial palsy (64%): acute motor axonal neuropathy (AMAN)
- Time between viral syndrome and GBS : 6 days (4-10 days)

N Engl J Med 2016; 375:1598-1601; Lancet. 2016; 387(10027): 1531-1539

Zika virus diseases in Thailand

- Among 1717 symptomatic patients, 2016-2017,
 - 21% were confirmed to have Zika virus infection
- Symptomatic individuals had 2.8 times the odds of testing positive for ZKV infection if they were from the same district and were sick within the same year of a confirmed ZKV



29 from 60 provinces

Lancet Infect Dis. 2019 Feb 27. pii: S1473-3099(18)30718-7

Zika virus diseases in Thailand

- Zika virus: circulated at a low sustained level for at least 16 years
- Case-based surveillance among children, adults, pregnant women, infants with congenital Zika syndrome (CZS) and GBS
- ZIKV cases peaked approximately 3 weeks following peak dengue virus transmission in both years
- 121 confirmed cases in pregnant women in 2016-2017
 - 45% of which were asymptomatic infections

Buathong R, et al. Am J Trop Med Hyg 2015;93(2):380-383. Thailand Ministry of Health, Department of Disease Control. Zika reporting data. Accessible at: <http://www.ddc.moph.go.th>; Lancet Infect Dis. 2019 Feb 27. pii: S1473-3099(18)30718-7

Challenges of Zika virus diseases

- Majority of ZKV infection: asymptomatic or mild symptom
- 61 countries in six WHO regions have evidence of established competent *A. aegypti* vectors but have not yet documented ZIKV transmission → potential risk for ZIKV spreading
- Associated with neurological complication in pregnant woman
- Presence of sexual transmission

Prevention of *Aedes*-borne virus diseases

- Avoiding mosquito bites
 - Using mosquito repellent, permethrin treatment for clothing, bed nets, window screens
- Controlling the mosquito vector by integrated vector management (IVM)
 - Targeting eggs, larva, pupae
 - elimination of *A. aegypti* mosquito breeding sites (environmental management)
 - application of larvicides
 - Targeting adult mosquito
 - Targeted residual spraying: resting sites
 - Space spraying
 - Genetic engineering inducing sterility in male mosquitoes

SIID



Emergence of mosquito-born virus during COVID-19 epidemic

- Disrupted routine fogging to eliminate mosquito breeding grounds
- More urban residents are stuck indoors during home quarantine
- Worried about COVID-19 when seeking out medical assistance at hospitals

SIID

Conclusion

- Diseases transmitted by *Aedes* mosquitoes are expanding
- The symptoms, vectors and geographic distribution of the arboviruses DENV, ZIKV and CHIKV overlap considerably
 - Point-of-care multiplex diagnostics are needed
- Need to strengthen intensive vector control

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THANK YOU